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Stereoselective synthesis of tarchonanthuslactone via the Prins cyclisation

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Abstract—The stereoselective total synthesis of tarchonanthuslactone, a polyketide natural product, has been achieved. The synthesis exploits the high stereochemical control in the Prins cyclisation along with ring closing metathesis (RCM) as a key step.

1. Introduction

Many polyketide natural products possessing *syn*- and *anti*-1,3-diols[1] along with 5,6-pyrone units exhibit various biological activities like plant growth inhibition as well as antifeedant, antifungal, antibacterial and antitumour properties.[2,3] Due to this wide spectrum of biological properties, several synthetic approaches have been reported for their synthesis.[4] Some such natural products are strictifolione **1**,[5a] passifloricin A **2**,[5b] pironetin **3**[5c] and cryptocarya diacetate **4**[5d] (Fig. 1). A representative example of this class is tarchonanthuslactone **5**, an α,β-unsaturated δ-lactone, isolated by Bohlmann from the leaves of a tree called *Tarchonanthus trilobus* in 1979.[6] Its absolute configuration was later established by Nakata et al. by asymmetric synthesis.[7k] Hsu et al. revealed that tarchonanthuslactone lowers plasma glucose in diabetic rats.[8] Owing to this interesting biological activity, there have been several approaches reported for the synthesis of tarchonanthuslactone.[7] In this paper, we describe a stereoselective synthesis of tarchonanthuslactone via Prins cyclisation.

The Prins cyclisation has been emerged as a powerful synthetic tool for the construction of multisubstituted tetrahydropyran system[9] and has been utilised in the synthesis of several natural products.[10] We have recently explored the utility of Prins cyclisation in the synthesis of various polyketide intermediates and applied it in the synthesis of some natural products.[11] As a part of this ongoing programme, we investigated the synthesis of tarchonanthuslactone.

In our retrosynthetic analysis (Fig. 2), we envisioned that the target molecule could be achieved from **14** through ring closing metathesis (RCM) and esterification with relevant

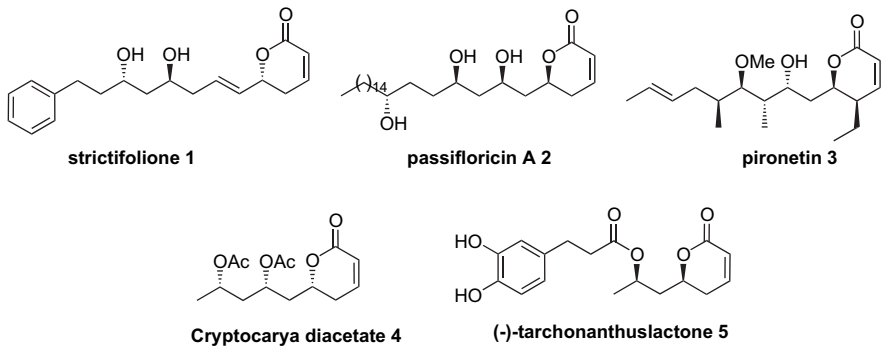

Figure 1.

Keywords: 5,6-Pyrones; Prins cyclisation; Ring closing metathesis.
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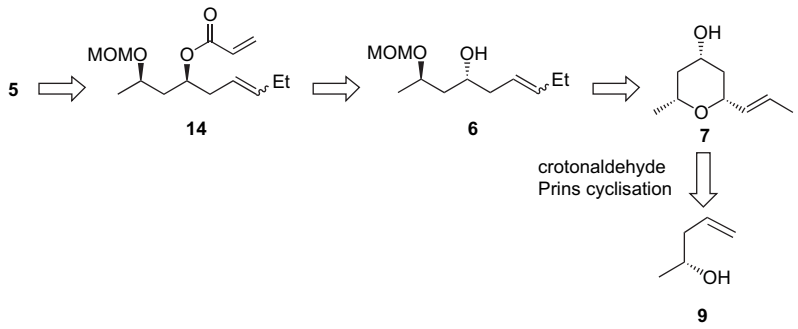
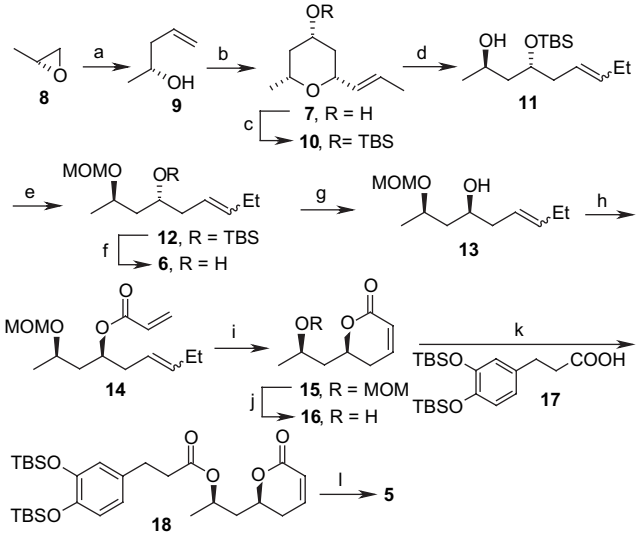


Figure 2.

aromatic fragment. Compound **14** was viewed to obtain from **6** via Mitsunobu inversion. It was proposed to obtain the 1,3-diol **6** from **7** via allylic cleavage and in turn **7** would be obtained via Prins cyclisation of homoallylic alcohol **9** and crotonaldehyde.

2. Results and discussion

The synthesis of tarchonanthuslactone is described in Scheme 1. Cu mediated opening[12] of epoxide in (*R*)-propylene oxide **8** (obtained via Jacobson's HKR methodology)[13] with vinyl magnesium bromide yielded homoallylic alcohol **9**.[14] The Prins cyclisation of **9** with crotonaldehyde in presence of TFA followed by hydrolysis of the resulting trifluoroacetate yielded tetrahydropyran **7** in 70% yield. TBS protection of **7** with TBSCl, DMAP and imidazole provided the corresponding TBS ether **10**, which when treated with Na in liquid ammonia underwent clean allylic cleavage to furnish 1,3-diol **11** in 90% yield. Diol **11** after protecting as its MOM ether **12** and cleavage of the TBS group in the presence of TBAF afforded alcohol **6**. Alcohol **6** when subjected to standard Mitsunobu inversion conditions (DEAD, PPh_3, *p*-nitrobenzoic acid in THF then K_2CO_3 in MeOH)[15] yielded **13** with required *syn*-1,3-diol system. Alcohol **13** was then transformed into its acrylic ester **14** and subjected to RCM in the presence of Grubbs' G2[16a,b] to furnish **15**. Of note was the failure of the RCM reaction with Grubbs' G1[16c] catalyst; the failure of which may be attributed to the presence of an internal double bond. Deprotection of MOM ether **15** using TFA in CH_2Cl_2 (1:5) provided the corresponding alcohol **16**, which on esterification with acid **17**[7h] in the presence of DCC and DMAP yielded ester **15**. Deprotection of the TBS groups in **18** using TBAF in THF furnished the target molecule **5**, which in all respects was identical to the reported natural product.[7h]



Scheme 1. Reagents and conditions: (a) CH_2=CHMgBr, CuBr, THF, −78 °C to −40 °C, 6 h, 80%; (b) crotonaldehyde, TFA, CH_2Cl_2, rt, 4 h, then K_2CO_3, MeOH, rt, 1 h, 70%; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C–rt, 4 h, 92%; (d) Na, liquid NH_3, THF, −33 °C, 45 min, 90%; (e) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C–rt, 4 h, 92%; (f) TBAF, THF, 0 °C–rt, 4 h, 94%; (g) *p*-$NO_2CH_2CO_2H$, DEAD, Ph_3P, THF, 0 °C–rt, 30 min, then K_2CO_3, MeOH, rt, 4 h, 75%; (h) acryloyl chloride, TEA, DMAP, CH_2Cl_2, 0 °C–rt, 1 h, 84%; (i) Grubbs' G2 catalyst, CH_2Cl_2, rt, 12 h, 60%; (j) TFA/CH_2Cl_2 (1:5), 0 °C–rt, 2 h, 85%; (k) **17**, DCC, DMAP, 5 h, 0 °C–rt, 83% and (l) TBAF, benzoic acid, THF, rt, 1 h, 82%.

3. Conclusion

In conclusion, we proved the versatility of the Prins cyclisation in natural product synthesis by achieving the total synthesis of tarchonanthuslactone **5**. Further applications of the Prins cyclisation in the synthesis of natural products are in progress and will be disclosed in due course.

4. Experimental

4.1. General

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh size silica gel. Mass spectra were obtained on Finnegan MAT 1020B or micro mass VG 70-70H spectrometer operating at 70 eV using a direct inlet system.

4.1.1. (*R*)-4-Penten-2-ol 9. To a solution of magnesium (6.7 g, 275 mmol) in dry THF (220 mL) at room temperature

were sequentially added 1,2-dibromoethane (0.6 mL, 6.85 mmol) and freshly prepared vinyl bromide (19.6 mL, 275 mmol) in a dropwise manner. CuCN (617 mg, 6.85 mmol) was added after allowing the reaction mixture to stir for 0.5 h. Then the mixture was cooled to −78 °C and propylene oxide **8** (8.0 g, 137 mmol) in THF (30 mL) was added and the mixture warmed to −40 °C. After stirring the mixture for 4 h at −40 °C, saturated NH_4Cl solution (100 mL) was added and the mixture extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (12% EtOAc/hexane) afforded **9** (9.48 g, 80%) as a colourless liquid. R_f=0.45 (SiO_2, 20% EtOAc in hexane); $[\alpha]_D^{20}$ +10.2 (*c* 2.5, Et_2O) (lit.:[14] 10.86 (*c* 3.2, Et_2O)); IR (Neat): ν=3447, 2924, 1635, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.84–5.56 (m, 1H), 5.10–4.91 (m, 2H), 3.83–3.67 (m, 1H), 2.73–2.33 (br s, 1H), 2.11 (t, 2H, *J*=6.7 Hz), 1.08 (d, 3H, *J*=5.9 Hz); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 134.7, 117.3, 66.7, 43.4, 22.4; MS (ESI): *m*/*z* 87 $(M+H)^+$.

4.1.2. (2*R*,4*S*,6*R*)-Tetrahydro-2-methyl-6-[(*E*)-prop-1-enyl]-2*H*-pyran-4-ol 7. Trifluoroacetic acid (53.7 mL, 697 mmol) was added slowly to a solution of the homoallylic alcohol **9** (2.0 g, 23 mmol) and crotonaldehyde (4.88 g, 69 mmol) in CH_2Cl_2 (90 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 4 h and then saturated aqueous sodium hydrogen carbonate solution (100 mL) was added and the pH was adjusted to >7 by the addition of triethylamine. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (4×40 mL) and the organic layers were combined, dried and the solvent was removed under reduced pressure. The residue was dissolved in methanol (30 mL) and stirred with potassium carbonate (6.4 g, 46 mmol) for 1 h. After removing MeOH under reduced pressure, water (30 mL) was added. The mixture was extracted with dichloromethane (3×30 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Column chromatography (15% EtOAc/hexane) afforded pure product **7** (3.89 g, 70% yield) as a colourless liquid. R_f=0.15 (SiO_2, 20% EtOAc in hexane); $[\alpha]_D^{25}$ +8.78 (*c* 2.25, $CHCl_3$); IR (Neat): ν=3441, 2924, 2853, 1636, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.64 (dt, 1H, *J*=15.4, 6.2 Hz), 5.48 (dd, 1H, *J*=15.4, 6.2 Hz), 3.82–3.67 (m, 2H), 3.52–3.38 (m, 1H), 1.96–1.87 (m, 2H), 1.71 (d, 3H, *J*=6.2 Hz), 1.39 (br s, 1H), 1.26–1.04 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 131.4, 127.4, 76.0, 71.4, 67.8, 42.6, 40.8, 21.6, 17.6; MS (ESI): *m*/*z* 157 $(M+H)^+$. Anal. Calcd for $C_9H_{16}O_2$ (156.22): C, 69.20; H, 10.32%. Found: C, 68.91; H, 9.98%.

4.1.3. (2*R*,4*S*,6*R*)-Tetrahydro-2-methyl-6-[(*E*)-prop-1-enyl-2*H*-pyran-4-yloxy](*tert*-butyl)-dimethylsilane 10. To a solution of **7** (2.10 g, 13.4 mmol) in dry CH_2Cl_2 (30 mL) were added catalytic DMAP (10 mg) and imidazole (1.37 g, 20.0 mmol) in one portion followed by TBSCl (2.43 mg, 16.0 mmol) in three portions at 0 °C. The reaction mixture was stirred for 4 h and slowly warmed to room temperature. It was then quenched by the addition of saturated NH_4Cl solution (15 mL), diluted with CH_2Cl_2 (30 mL), washed with brine (15 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude by column chromatography (3% EtOAc/hexane) afforded TBS ether **10** (3.34 g, 92%) as a colourless oil. R_f=0.7 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{25}$ +2.32 (*c* 2.0, $CHCl_3$); IR (Neat): ν=2933, 2856, 1635, 1078, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.64 (dt, 1H, *J*=15.6, 6.2 Hz), 5.44 (dd, 1H, *J*=15.6, 6.2 Hz), 3.82–3.58 (m, 2H), 3.51–3.28 (m, 1H), 1.87–1.62 (m, 5H), 1.29–1.05 (m, 5H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 131.7, 127.3, 76.2, 71.5, 68.7, 43.2, 41.4, 25.8, 21.8, 18.0, 17.7, −4.5; MS (ESI): *m*/*z* 293 $(M+Na)^+$, 271 $(M+H)^+$. Anal. Calcd for $C_{15}H_{30}O_2Si$ (270.48): C, 66.61; H, 11.18%. Found: C, 66.27; H, 11.09%.

4.1.4. (*E*/*Z*,2*R*,4*R*)-2-(Hydroxy)non-6-en-4-yloxy(*tert*-butyl)dimethylsilane 11. To a solution of sodium (1.53 g, 66 mmol) in liquid NH_3 (15 mL) was added TBS ether **10** (1.8 g, 6.6 mmol) in dry THF (8 mL). The mixture was stirred for 45 min at −33 °C and then solid NH_4Cl (3.56 g, 66 mmol) was added after cooling the mixture to −78 °C. NH_3 was allowed to evaporate and the residual mixture was taken up in ethyl acetate (20 mL) and washed with water (8 mL), brine (8 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and chromatography (20% EtOAc/hexane) of the crude afforded **11** (1.38 g, 90% yield) as a colourless liquid. R_f=0.2 (SiO_2, 25% EtOAc in hexane); IR (Neat): ν=3445, 2929, 2856, 1633, 1064, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.53–5.20 (m, 2H), 4.20–4.02 (m, 1H), 3.99–3.85 (m, 1H), 2.11–1.89 (m, 2H), 1.67–1.46 (m, 4H), 1.30–1.10 (m, 5H), 0.99–0.87 (m, 12H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 135.0, 131.0, 125.0, 124.4, 71.8, 67.7, 67.5, 64.4, 44.2, 37.5, 28.6, 25.7, 25.6, 23.8, 22.8, 17.9, 17.8, −4.5, −4.8, −5.0; MS (LSI): *m*/*z* 295.2 $(M+Na)^+$, 273.1 $(M+H)^+$. Anal. Calcd for $C_{15}H_{32}O_2Si$ (272.50): C, 66.12; H, 11.84%. Found: C, 65.38; H, 11.53%.

4.1.5. (*E*/*Z*,2*R*,4*R*)-2-(Methoxymethoxy)non-6-en-4-yloxy(*tert*-butyl)dimethylsilane 12. To alcohol **11** (1.5 g, 5.5 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0 °C were added diisopropylethylamine (2.13 g, 16.5 mmol), catalytic DMAP (8 mg) and MOMCl (0.88 g, 11.0 mmol) successively and the mixture was stirred for 4 h at room temperature, quenched by adding water (8 mL) and extracted with CH_2Cl_2 (3×8 mL). The organic extracts were washed with brine (8 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to remove the solvent and the crude residue was purified by column chromatography (6% EtOAc/hexane) to afford the MOM ether **12** (1.6 g, 92%) as colourless oil. R_f=0.4 (SiO_2, 10% EtOAc in hexane); IR (Neat): ν=2930, 2857, 1635, 1042, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.52–5.29 (m, 2H), 4.66–4.55 (m, 2H), 4.00–3.57 (m, 2H), 3.34 (s, 1.5H), 3.33 (s, 1.5H), 2.09–1.96 (m, 2H), 1.67–1.41 (m, 4H), 1.18–1.12 (m, 3H), 1.01–0.82 (m, 12H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 131.2, 130.9, 125.0, 124.7, 96.0, 95.4, 75.5, 71.4, 69.1, 65.8, 55.5, 55.2, 43.2, 41.2, 37.7, 35.2, 28.1, 27.8, 25.8, 24.5, 17.8, 13.7, 10.9, −3.9, −4.1, −4.5; MS (LSI): *m*/*z* 339.2 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{36}O_3Si$ (316.55): C, 64.50; H, 11.46%. Found: C, 64.14; H, 11.24%.

4.1.6. (*E*/*Z*,2*R*,4*R*)-2-(Methoxymethoxy)non-6-en-4-ol 6. To an ice cold solution of **12** (1.5 g, 4.70 mmol) in dry THF (10 mL) was added TBAF (5.67 mL, 1 M in THF,

5.64 mmol). After 15 min of stirring, reaction mixture was brought to room temperature and stirred for another 4 h. The reaction mixture was cooled to 0 °C and quenched with saturated NH_4Cl solution (5 mL), extracted with ethyl acetate (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (25% EtOAc/hexane) to afford the alcohol **6** (902 mg, 94% yield) as a colourless liquid. R_f=0.4 (SiO_2, 40% EtOAc in hexane); IR (Neat): ν=3447, 2926, 1736, 1638, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.54–5.26 (m, 2H), 4.75–4.56 (m, 2H), 4.14–3.67 (m, 2H), 3.40 (s, 1.5H), 3.39 (s, 1.5H), 2.35–1.93 (m, 2H), 1.66–1.36 (m, 4H), 1.26–1.12 (m, 3H), 1.04–0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 130.5, 125.2, 124.3, 124.0, 96.1, 95.3, 75.6, 71.3, 71.1, 67.4, 63.9, 55.6, 55.4, 42.8, 40.8, 37.9, 34.6, 28.3, 25.5, 20.5, 20.3, 17.7; MS (LSI): *m/z* 225.1 $(M+Na)^+$. Anal. Calcd for $C_{11}H_{22}O_3$ (202.29): C, 65.31; H, 10.96%. Found: C, 65.45; H, 10.73%.

4.1.7. (*E/Z*,2*R*,4*S*)-2-(Methoxymethoxy)non-6-en-4-ol 13. To a stirred mixture of **6** (1.1 g, 5.4 mmol), triphenylphosphine (4.56 g, 17.4 mmol) and *p*-nitrobenzoic acid (1.18 g, 7.0 mmol) in dry THF (20 mL) at 0 °C was added diethylazodicarboxylate (3.03 g, 17.4 mmol) via a syringe. The reaction mixture was then stirred for 0.5 h at room temperature, diluted with water (10 mL) and extracted with ethyl acetate (2×15 mL). After removing the solvent, the crude residue was dissolved in MeOH (10 mL) and K_2CO_3 was added (1.5 g, 10.8 mmol). After stirring the mixture for 4 h at room temperature, it was diluted with water (15 mL) and extracted with CH_2Cl_2 (3×10 mL). Removal of solvent under reduced pressure followed by flash chromatography (25% EtOAc/hexane) afforded **13** (825 mg, 75% yield) as a colourless liquid. R_f=0.4 (40% EtOAc in hexane); IR (Neat): ν=3445, 2962, 2932, 1608, 1100, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.59–5.19 (m, 2H), 4.83–4.53 (m, 2H), 4.05–3.64 (m, 2H), 3.38 (s, 1.5H), 3.37 (s, 1.5H), 3.06 (br s, 1H), 2.37–1.94 (m, 3H), 1.80–1.41 (m, 3H), 1.30–0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 134.1, 130.5, 124.7, 123.9, 95.1, 94.4, 73.4, 73.0, 67.1, 55.7, 55.5, 44.1, 43.2, 40.7, 37.6, 28.4, 25.5, 23.4, 20.6, 20.2, 17.7; MS (LSI): *m/z* 225.1 $(M+Na)^+$. Anal. Calcd for $C_{11}H_{22}O_3$ (202.29): C, 65.31; H, 10.96%. Found: C, 65.08; H, 10.61%.

4.1.8. (*E/Z*,2*R*,4*S*)-2-(Methoxymethoxy)non-6-en-4-yl-acrylate 14. The alcohol **13** (600 mg, 2.97 mmol) was dissolved in 10 mL of CH_2Cl_2 and to the solution was added sequentially catalytic DMAP (5 mg), acryloyl chloride (403 mg, 4.45 mmol) and Et_3N (0.54 mL, 5.94 mmol) at 0 °C. After stirring the reaction mixture for 1 h at room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine (10 mL) and concentrated in vacuo. The residue was purified by column chromatography (4% EtOAc/hexane) to afford **14** (638 mg, 84% yield) as a colourless liquid. R_f=0.6 (SiO_2, 10% EtOAc in hexane); IR (Neat): ν=2930, 1637, 1405, 1197, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.37 (dd, 1H, *J*=18.7, 1.5 Hz), 6.14–6.02 (m, 1H), 5.83–5.77 (m, 1H), 5.55–5.27 (m, 2H), 4.66–4.52 (m, 3H), 3.73–3.53 (m, 1H), 3.36 (s, 1.5H), 3.35 (s, 1.5H), 2.33–2.15 (m, 1H), 2.11–1.84 (m, 2H), 1.70–1.50 (m, 3H), 1.36–1.15 (m, 4.5H), 1.01–0.93 (m, 1.5H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 165.5, 135.8, 135.3, 134.7, 134.0, 130.6, 128.9, 125.5, 125.2, 124.2, 95.5, 94.8, 74.2, 71.3, 70.4, 55.5, 55.2, 41.4, 40.6, 37.5, 34.2, 28.1, 25.6, 20.3, 20.0, 17.7, 13.6; MS (ESI): *m/z* 279 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{24}O_4$ (256.34): C, 65.60; H, 9.44%. Found: C, 65.33; H, 9.27%.

4.1.9. (*S*)-5,6-Dihydro-6-[(*R*)-2-(methoxymethoxy)propyl]pyran-2-one 15. Grubbs' G2 catalyst (66.3 mg, 5 mol %) was dissolved in 10 mL of degassed CH_2Cl_2 and was added dropwise to a solution of the acrylic ester **14** (400 mg, 1.56 mmol) in 40 mL of degassed CH_2Cl_2. The reaction mixture was stirred at room temperature for 12 h by which time all of the starting material was consumed (TLC). The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography (20% EtOAc/hexane) to obtain **15** (187 mg, 60% yield) as a colourless oil. R_f=0.3 (SiO_2, 30% EtOAc in hexane); $[\alpha]_D^{25}$ −6.5 (*c* 0.5, $CHCl_3$); IR (Neat): ν=2925, 2853, 1718, 1648, 1247, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.85 (ddd, 1H, *J*=9.8, 5.2, 3.0 Hz), 6.01 (dt, 1H, *J*=9.8, 1.5 Hz), 4.64 (d, 1H, *J*=6.7 Hz), 4.63–4.53 (m, 2H), 3.97–3.84 (m, 1H), 3.33 (s, 3H), 2.42–2.28 (m, 1H), 2.19–2.07 (m, 1H), 1.80–1.55 (m, 2H), 1.25 (d, 3H, *J*=6.5 Hz); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 164.1, 144.8, 121.5, 96.1, 75.2, 69.7, 55.4, 41.8, 29.4, 20.1; MS (ESI): *m/z* 223.1 $(M+Na)^+$, 201.0 $(M+H)^+$. Anal. Calcd for $C_{10}H_{16}O_4$ (200.23): C, 59.99; H, 8.05%. Found: C, 59.62; H, 7.81%.

4.1.10. [5(*S*),7(*R*)]-7-Hydroxy-5-(oct-2-enolide) 16. Compound **15** (200 mg, 1.0 mmol) dissolved in CH_2Cl_2 (1.8 mL) and then TFA (456 mg, 4 mmol) was added dropwise at room temperature. After stirring the mixture at the same temperature for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution (8 mL) and extracted with CH_2Cl_2 (2×8 mL). The combined organic extracts were washed with brine (8 mL), concentrated in vacuo and the residue subjected to column chromatography (20% EtOAc/hexane) to afford alcohol **16** (132 mg, 85% yield) as a colourless oil. R_f=0.3 (SiO_2, 30% EtOAc in hexane); $[\alpha]_D^{25}$ −111 (*c* l, $CHCl_3$); IR (Neat): ν=3422, 2925, 2855, 1712, 1387, 1253, 1117, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.9 (ddd, *J*=10.0, 8.5, 4.0 Hz), 6.0 (dt, 1H, *J*=10.0, 2.0 Hz), 4.82–4.53 (m, 1H), 4.35–4.00 (m, 1H), 2.28–2.49 (m, 2H), 2.10–1.45 (m, 2H), 1.24 (d, 3H, *J*=6.0 Hz); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 164.2, 145.5, 121.2, 76.8, 65.2, 43.3, 29.8, 23.7; MS (ESI): *m/z* 157 $(M+H)^+$. Anal. Calcd for $C_8H_{12}O_3$ (156.18): C, 61.52; H, 7.74%. Found: C, 61.29; H, 7.43%.

4.1.11. 3′,4′-Bis(*tert*-butyldimethylsilyloxy)hydrocinnamic acid 17. To a stirred solution of 3′,4′-dihydroxyhydrocinnamic acid (900 mg, 2.2 mmol) in dry DMF (10 mL) were added imidazole (1.34 g, 19.8 mmol) and *tert*-butyldimethylsilyl chloride (1.49 g, 10 mmol). After 48 h at room temperature, the mixture was diluted with ether (40 mL) and water (10 mL). The mixture was stirred until a clear phase-separation appeared and then extracted with ether (4×40 mL). The combined organic layers were washed with saturated NH_4Cl (3×100 mL) and brine (2×100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel column chromatography (15% EtOAc/hexane) of the residue gave the acid **17** as a white solid (846 mg,

94% yield). Mp 87–88 °C; R_f=0.2 (SiO_2, 20% EtOAc in hexane); IR (Neat): ν=3060, 2840, 1710, 1600, 1575, 1500, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.74 (d, 1H, J=8.0 Hz), 6.67 (d, 1H, J=2 Hz), 6.63 (dd, 1H, J=8.0, 2.0 Hz), 2.84 (t, 2H, J=7.5 Hz), 2.62 (t, 2H, J=7.5 Hz), 0.98 (s, 18H), 0.18 (s, 12H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 179.6, 146.7, 145.3, 133.3, 121.1, 121.0, 35.9, 29.9, 25.9, 18.4, −4.1; MS (ESI): m/z 428.6 $(M+NH_4)^+$. Anal. Calcd for $C_{21}H_{38}O_4Si_2$ (410.69): C, 61.42; H, 9.33%. Found: C, 61.04; H, 8.95%.

4.1.12. [5(*S*),7(*R*)]-7-[*S*-(Oct-2-enolide)3′,4′-tris(*tert*-butyldimethylsilyloxy)]dihydrocinnamate 18. To a solution of alcohol **16** (106 mg, 0.68 mmol) in CH_2Cl_2 (20 mL) were added acid **17** (308 mg, 0.75 mmol) and DCC (155 mg, 0.75 mmol) at room temperature. DMAP (41 mg, 0.34 mmol) was then added and stirring continued for 15 h. Filtration of the reaction mixture, evaporation of the solvent and column chromatography (15% EtOAc/hexane) of the resulting crude afforded ester **18** (312 mg, 83% yield) as a colourless oil. R_f=0.2 (SiO_2, 20% EtOAc in hexane); $[\alpha]_D^{25}$ −44 (*c* 1, $CHCl_3$); IR (Neat): ν=2960, 2860, 1740, 1690, 1600, 1575, 1500, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.80 (ddd, 1H, J=10, 5.5, 3.0 Hz), 6.68 (d, 1H, J=8.0 Hz), 6.63 (d, 1H, J=2.0 Hz), 6.58 (dd, 1H, J=8.0, 2.0 Hz), 5.96 (ddd, 1H, J=10, 2.0, 1.0 Hz), 5.07 (ddq, 1H, J=8.0, 6.5, 6.0 Hz), 4.39 (m, 1H), 2.78 (t, 2H, J=7.5 Hz), 2.52 (t, 2H, J=7.5 Hz), 2.40–2.21 (m, 2H), 1.94 (m, 2H), 1.22 (d, 3H, J=6 Hz), 0.95 (s, 12H), 0.94 (s, 3H), 0.16 (s, 12H), 0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 172.3, 163.8, 146.5, 145.1, 144.7, 133.3, 121.17, 121.02, 120.97, 120.76, 74.8, 67.0, 40.7, 36.1, 30.1, 29.0, 25.8, 20.2, 18.3, −4.2; MS (ESI): m/z 549 $(M+H)^+$. Anal. Calcd for $C_{29}H_{48}O_6Si_2$ (548.86): C, 63.46; H, 8.81%. Found: C, 62.51; H, 8.57%.

4.1.13. Tarchonanthuslactone 5. A solution of compound **18** (272 mg, 0.49 mmol) in THF (20 mL) was treated with benzoic acid (180 mg, 0.15 mmol) and with a 1.1 M solution of TBAF in THF (4.5 mL, 5 mmol) and then stirred at room temperature for 1 h. The solvent was evaporated and AcOEt (20 mL) and water (20 mL) were added to the residue. The aqueous layer was saturated with sodium chloride and extracted with AcOEt (4×30 mL). The combined organic layers were washed with water (2×50 mL) and brine (2×50 mL), dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by column chromatography (ether) to give tarchonanthuslactone **5** (130 mg, 82% yield) as a white solid. Mp 89–90 °C (lit.:[7h] 89–90 °C); R_f=0.32 (ether); $[\alpha]_D^{25}$ −81 (*c* 0.35, $CHCl_3$) (lit.:[7h] −83 (*c* 0.4, $CHCl_3$)); IR (Neat): ν=3341, 2925, 2853, 1715, 1606, 1522, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.80 (ddd, 1H, J=10.0, 6.0, 3.0 Hz), 6.73 (d, 1H, J=8.0 Hz), 6.7 (d, 1H, J=2.0 Hz), 6.53 (br s, 2H), 6.53 (dd, 1H, J=8.0, 2.0 Hz), 5.96 (ddd, 1H, J=10.0, 2.0, 1.0 Hz), 5.04 (qdd, 1H, J=8.0, 7.0, 6.5 Hz), 4.21 (dddd, 1H, J=11.0, 6.5, 4.5, 6.0 Hz), 2.79 (t, 2H, J=7.0 Hz), 2.57 (t, 2H, J=7.0 Hz), 2.34–2.13 (m, 2H), 1.89 (m, 2H), 1.21 (d, 3H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 75.467 MHz): δ 173.0, 165.3, 146.0, 144.0, 142.4, 132.4, 120.5, 120.1, 115.2, 75.2, 67.2, 40.5, 36.0, 30.1, 28.8, 20.2. MS (ESI): m/z 321 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}O_6$ (320.33): C, 63.74; H, 6.29%. Found: C, 63.37; H, 6.08%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.019.

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